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ABERRANT PROMOTER METHYLATION CAN BE USEFUL AS A MARKER OF RECURRENT DISEASE IN PATIENTS WITH CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE III

Ana Paula Sarreta Terra[1], Eddie Fernando Candido Murta[2], Paulo José Maluf[2], Otávia Luísa Silva Damas Caballero[3], Mariana Brait[3], and Sheila Jorge Adad[1]

[1]Discipline of Special Pathology, [2]Discipline of Gynecology and Obstetrics, Research Institute of Oncology (IPON), [3]Ludwig Institute of Cancer Research, Federal University of Triângulo Mineiro (UFTM), Uberaba, Brazil

Introduction: **Although studies of risk factor profiles have been conducted to identify biological markers to predict the natural history of cervical intraepithelial neoplasia (CIN) grade III, there is not sufficient information to support the routine clinical use of any biomarker.**
Objectives: **The purpose of this study was to examine aberrant promoter methylation, which is implicated in cancer development and progression, in CIN III lesions in order to identify markers associated with more aggressive biological behavior that could be used to recognize women who are at higher risk of recurrence.**
Patients and methods: **We used methylation-specific polymerase chain reaction to analyze promoter hypermethylation of 8 genes (*p16, RARβ, GSTP1, MGMT, p14, TIMP3, E-cad* and *DAPk*) in 33 uterine cervix cones with CIN III that were also submitted to human papillomavirus (HPV) genotyping. All 33 patients in this study had been clinically followed after conization with Papanicolaou smears, colposcopy, and biopsy when indicated, every 6 months during 5 years.**
Results: **Of the 33 patients, 12 (36%) underwent immediate hysterectomy after conization for having compromised cone margins, 14 (43%) have not relapsed, and 7 (21%) presented CIN relapse. The frequency of HPV infection in this group was 97% and no significant difference between the groups was observed. HPV of high oncogenic risk was present in 29 (87.9%) cases; HPV 16 was the most frequent (69.7%), while HPV 18 was found in 33.3%; however, it was associated with HPV 16 in 15.1%. Concomitant infection by HPV 6/11 was detected in 21.2% (15.1% with HPV 16 and 6.1 with HPV 18). 85.7% (6/7) of patients with recurrence had HPV 18 *vs* 0% (0/14) of patients without recurrence (*P* = 0.0001). At least 1 of the 8 genes was found hypermethylated in all samples. Concomitant hypermethylation of several genes was frequently found. However, CIN relapse was only seen in the cases with hypermethylation of 3 or more of the 8 genes studied (*P* = 0.0039).**
Conclusion: **We suggest that aberrant promoter methylation may play a role and may serve as a useful biomarker in the recurrence of CIN.**

Key words: cervical intraepithelial neoplasia grade III, *p16, RARβ, GSTP1, MGMT, p14, TIMP3, E-cad, DAPk,* human papillomavirus, methylation, recurrence.

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Correspondence to: Eddie Fernando Candido Murta, Research Institute of Oncology (IPON)/Discipline of Ginecology e Obstetrics, Federal University of Triângulo Mineiro (UFTM), Avenida Getúlio Guaritá, s/n, CEP 38025-440, Uberaba, MG, Brazil. Tel +55-34-3318 5326; fax +55-34-3318 5342; e-mail: eddiemurta@mednet.com.br or eddiemurta@pq.cnpq.br

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